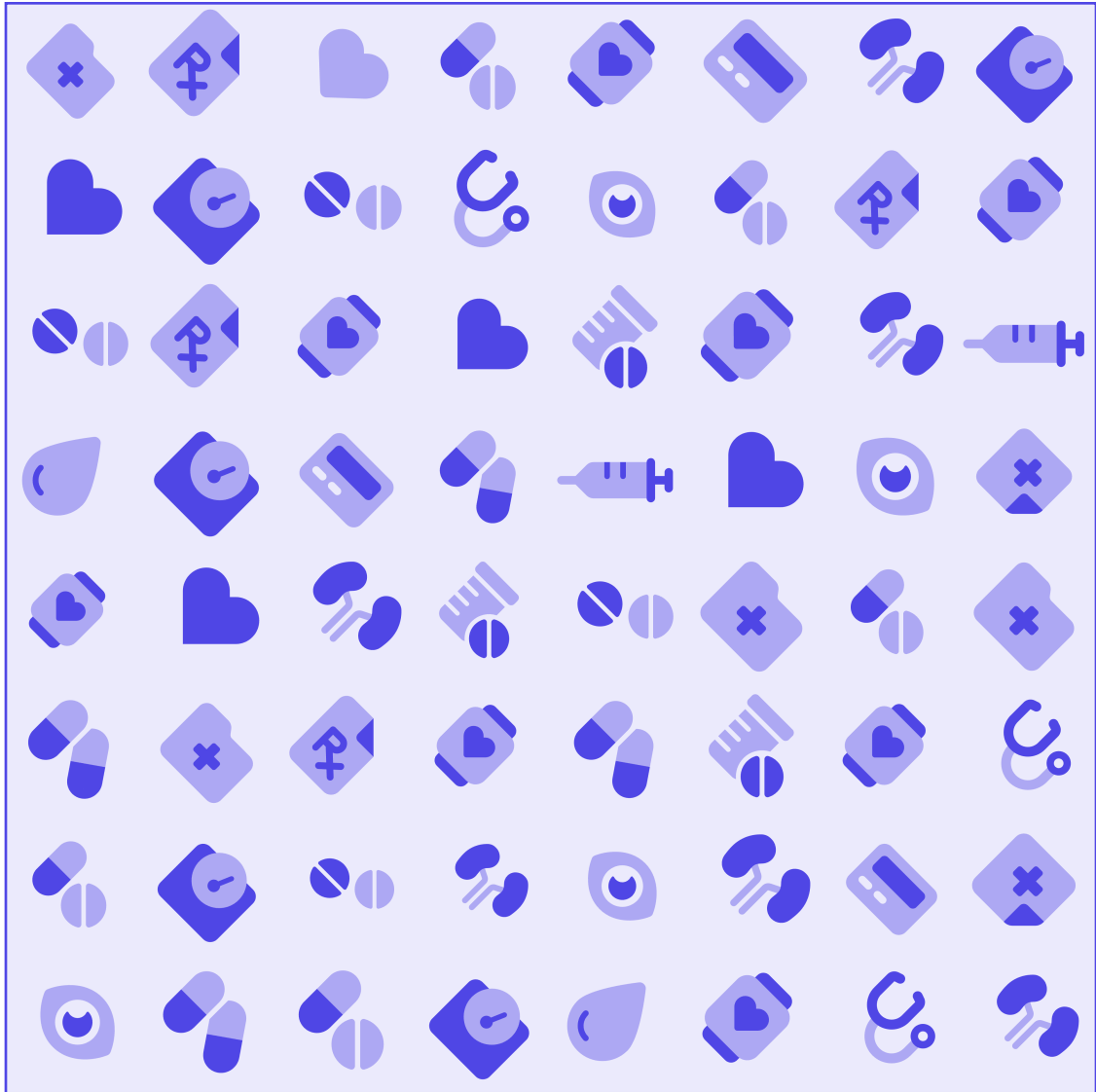




Pyrls Press — 2024

Type 2 Diabetes Pharmacotherapy



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Scope of Document

This document contains a collection of concise resources on the subject of glycemic-lowering pharmacotherapy for **adult patients** with **type 2 diabetes**. It is intended to be utilized as a supplemental resource for learning and/or referencing, and is not a comprehensive guide to all relevant information on the subject.

Disclaimer

Readers should note that this document was published in **January 2024**, and some of the information in this document is **subject to frequent change**.

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We thank you so much!

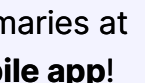
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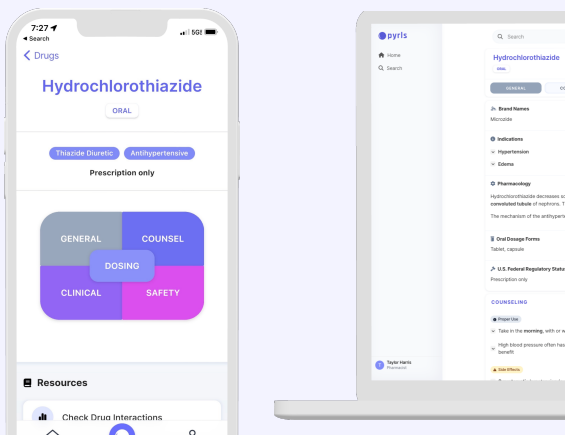


TABLE OF CONTENTS

Diagnostic Criteria and Screening for Type 2 Diabetes	1
Treatment Assessment and Goals	3
Estimated Average Glucose	4
Continuous Glucose Monitors (CGMs)	5
Comparison of CGMs	8
Overview of Hemoglobin A1C	10
T2DM Treatment Algorithm for Glycemic Control (2024 Update)	11
Insulin Classes and Action Profiles	13
Insulin Storage Requirements	14
Injection Areas	16
T2DM Drug Class Comparison	17
Diabetes Drugs: Cardiovascular and Renal Effects	18
Metformin: Dosing and Indications	20
GLP-1 RAs and GLP-1/GIP RA: Efficacy and Safety	21
GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications	22
SGLT2 Inhibitors: Efficacy and Safety	25
SGLT2 Inhibitors: Dosing and Indications	26

TABLE OF CONTENTS *(cont.)*

DPP-4 Inhibitors: Efficacy and Safety	27
DPP-4 Inhibitors: Dosing and Indications	28
Sulfonylureas: Efficacy and Safety	29
Sulfonylureas: Dosing and Indications	30
Thiazolidinediones: Efficacy and Safety	32
Thiazolidinediones: Dosing and Indications	32
Drugs that Cause Hyperglycemia	33
Drugs that Cause Hypoglycemia	34
Hypoglycemia Classification and Treatment	35
References	36

Diagnostic Criteria and Screening for Type 2 Diabetes

Diagnostic Criteria

CONDITION	A1C (%)	FPG* (mg/dL)	2-HR PG** (mg/dL)
Diabetes	≥6.5	≥126	≥200
Prediabetes	5.7 - 6.4	100 - 125	140 - 199

Recreated from Table 2.2 of the ADA Standards of Care in Diabetes - 2024
*Fasting plasma glucose (FPG) should be conducted after an 8+ hour fasting period
**Plasma glucose 2 hours after the administration of 75 grams of glucose during an oral glucose tolerance test (OGTT)

Tests used to diagnose diabetes include: **hemoglobin A1C (A1C)**, **fasting plasma glucose (FPG)** and **2-hour plasma glucose (2-HR PG)** during an oral glucose tolerance test.

The **plasma glucose values** (FPG and 2-HR PG) have **greater** diagnostic accuracy than A1C in patients with *discordant values* (e.g., A1C value is not elevated but FPG and/or 2-hour PG values are elevated).

However, A1C is **more convenient** than plasma glucose tests due to a lack of required fasting. Additionally, since it is an indirect measure of average blood glucose over a period of time (~3 months) it is **less affected** by glucose fluctuations or disturbances (due to stress, diet changes, illness, etc.).

In cases where there is evidence of discordance between A1C and plasma glucose values the **A1C value** must be considered **unreliable**. There are a number of possible underlying causes or conditions for this discrepancy, such as sickle cell disease, pregnancy and HIV. When an underlying cause is suspected or known, only **plasma glucose testing** (FPG or 2-HR PG) may be used for diagnostic purposes.

A diagnosis for diabetes requires **two abnormal screening results** (from the same or separate samples using the same or different test). In cases of separate samples it is recommended that the second test be performed as soon as possible. In cases of **discordant results** (e.g. A1C 6.2% and FPG 175 mg/dL) the test result above the diagnostic threshold should be repeated (in this example, FPG). If the test results are near the diagnostic threshold, testing should be repeated in **3-6 months**.

The only times when two abnormal tests are **not** required are in cases where there is *clear clinical evidence of diabetes*, such as classic symptoms of hyperglycemia/hyperglycemic crisis (e.g. polydipsia, polyuria, blurred vision) **plus** a random plasma glucose **≥200 mg/dL**. In these cases, repeat testing is **not** required.

Diagnostic Criteria and Screening for Type 2 Diabetes

Screening for Type 2 Diabetes

Screening should be considered for **overweight/obese*** adults with **one or more** of the following risk factors:

- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of cardiovascular disease
- Hypertension (BP $\geq 130/80$ mmHg or on antihypertensive therapy)
- HDL < 35 mg/dL and/or triglycerides > 250 mg/dL
- Polycystic ovary syndrome
- Physical inactivity
- Clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

**BMI ≥ 25 kg/m² (or ≥ 23 kg/m² in Asian American individuals)*

Patients with **prediabetes** (A1C 5.7-6.4%) should be screened **annually**. Patients with a history of **gestational diabetes** should be screened **every 3 years**. For all other patients, screening for diabetes should begin at an age of **35 years** and be repeated at least **every 3 years** (if results are normal).

Certain **medications** (e.g., glucocorticoids, statins, thiazide diuretics) may **increase** the risk for developing type 2 diabetes. It is reasonable to consider screening patients receiving these medications for prediabetes and diabetes.

Patients prescribed **second-generation antipsychotic medication** should be screened for prediabetes and diabetes at baseline, 12-16 weeks after initiation (sooner, if indicated) and then annually thereafter.

Patients with **HIV** should be screened for prediabetes and diabetes at baseline (prior to antiretroviral therapy) and when switching antiretroviral therapy (ART). Screening should repeat **3-6 months** after initiating or switching ART. If results are normal, screening should continue **annually**. In these patients, **FPG** is the recommended screening method.

Treatment Assessment and Goals

Treatment Assessment

The **primary metrics** for monitoring treatment of type 2 diabetes (T2DM) are **hemoglobin A1C** (A1C) and preprandial/postprandial glucose measurements.

In patients with diabetes, **hemoglobin A1C** and/or appropriate CGM metrics (e.g., time in range, time above/below range) should be assessed:

- At least **twice yearly** (e.g., every 6 months) in patients meeting their treatment goals and maintaining stable glycemic control. Those with frequent/severe hypo- or hyperglycemia, those with fluctuating health and pediatric patients undergoing growth and development may require more frequent monitoring (e.g., every 3 months).
- At least **quarterly** (e.g., every 3 months) and as needed in patients with recent therapy change, those not meeting their glycemic goals.

Preprandial and postprandial **plasma glucose levels** goals can help guide healthy diet practices, lifestyle changes, and pharmacotherapy selection and dosing.

Treatment Goals

The **primary goal** of therapy is **reducing** the patient's **A1C** to goal *without* causing hypoglycemic episodes.

Treatment goals must be **individualized** (and periodically reassessed) after taking into consideration comorbid conditions, hypoglycemia risk and other patient-specific characteristics.

POPULATION	A1C (%)	PREPRANDIAL	1-HR PPG	2-HR PPG
Most patients*	<7.0	80 - 130 mg/dL	- -	<180 mg/dL
Certain patients**	<8.0	- -	- -	- -
Pregnant***	<6.0	<95 mg/dL^	<140 mg/dL	<120 mg/dL

Recreated from Tables 6.3 and Recommendations 6.7, 15.7 and 15.8 of the ADA Standards of Care in Diabetes - 2024
*More strict goals may be reasonable if achievable without significant hypoglycemia risk
**Those at risk of or prone to severe hypoglycemia, limited life expectancy, important comorbidities, long duration of diabetes, or patients who prefer a less stringent A1C goal
***If A1C < 6% cannot be safely achieved, choosing a less strict goal of < 7% is reasonable to avoid hypoglycemic events
^Fasting plasma glucose

Deintensification of therapy for patients with **A1C between 6-7%** is **not** necessary if the hypoglycemia risk is **low**. However, if the concern for hypoglycemia is **significant** then deintensification may be warranted as any *long-term treatment benefit* may be outweighed by the *short-term risk*.

Patients that are **high-risk** for hypoglycemia that are receiving hypoglycemia-causing medication (e.g., insulin, sulfonylureas) should have said medication **de-intensified** or **switched** to an agent with a lower-risk for hypoglycemia.

Treatment Assessment and Goals (cont.)

Assessment & Modification Interval

The treatment regimen should be reassessed every **3-6 months** and modified if appropriate.

Generally, patients should be assessed every **3 months** while **not** at target glycemic goals and **every 6 months** while stable at goal. Treatment intensification for patients **not** at goal should not be delayed when possible.

Estimated Average Glucose

The table below provides **estimated average glucose levels** (eAG) for specific A1C values. This data can be used to *counsel patients* and *guide therapy*.

Patients are generally able to understand **blood glucose values** better than A1C. By discussing treatment goals with patients while including target eAG they can better understand their own glucose readings and overall glycemic control.

A1C (%)	AVERAGE GLUCOSE (mg/dL)
5	97 (76 - 120)
6	126 (100 - 152)
7	154 (123 - 185)
8	183 (147 - 217)
9	212 (170 - 249)
10	240 (193 - 282)
11	269 (217 - 314)
12	298 (240 - 347)

Recreated from Table 6.1 from the ADA Standards of Care in Diabetes - 2024

For example, if a patient's current A1C is **9.0%** their eAG would be **212 mg/dL**. Typically, an A1C goal of **< 7.0%** is appropriate for most patients (eAG < 154 mg/dL).

Encouraging the patient to achieve an **average glucose** of < 154 mg/dL can better enable them to track their own progress between office visits and A1C tests and more clearly see the benefits of positive lifestyle modifications (e.g., dietary changes, increased physical activity, weight loss).

Continuous Glucose Monitors (CGMs)

Continuous glucose monitors (CGMs) have been shown to **improve A1C levels**, time in range, and **reduce hypoglycemia** compared to standard blood glucose monitoring (e.g., "fingerstick" monitoring) alone in many studies.

For managing diabetes, there are different types of CGMs available, and the choice should depend on the individual's specific situation and preferences. Patients who are prescribed CGMs should receive regular **instruction** and **evaluation** of their CGM use, testing technique and glycemic management.

Most CGMs involve insertion of a small wire **sensor** under the skin on the back of the **upper arm** (*Senseonics Eversense E3 is implanted under the skin surgically*). Then a transmitter is used to deliver the glucose readings to a **receiver** or smart device. For certain CGMs (*such as the Freestyle Libre 2*), the receiver/smart device is actually used to intermittently scan the sensor and record the readings.

Blood Glucose Readings vs Sensor Glucose Readings

Patients using CGMs will occasionally check their blood glucose with a **fingerstick device**.

Blood glucose readings are taken from your **bloodstream**, providing a direct measurement of your **current** glucose levels.

Sensor glucose readings are obtained from the **interstitial fluid**, a fluid residing just beneath the skin. When carbohydrates are consumed, the body absorbs glucose into the bloodstream **before** it diffuses into the interstitial fluid.

This difference in the **source** of glucose readings causes there to be a **time lag** between the two. This **time lag** forms the basis for CGM's ability to provide not only **current** glucose readings but also an arrow **indicating** the direction in which glucose levels are headed.

It is important to educate patients about the **differences** between blood glucose and sensor glucose readings. Doing so helps them understand that these values won't always align perfectly and can prevent patients from losing trust in their CGM device due to perceived inconsistencies between the two readings.

The **warm-up time** for CGMs is **not** the same as the lag time, although they are related concepts. The warm-up time refers to the **initial period** when a CGM sensor is activated before it starts providing **accurate** and **reliable** glucose readings. The duration of the warm-up time can vary depending on the specific CGM system but typically ranges from 30 minutes to a few hours.

Continuous Glucose Monitors *(cont.)*

Real-time CGMs vs Intermittently Scanned CGMs

Real-time CGMs (rtCGMs) and **intermittently scanned CGMs** (isCGMs) both measure blood glucose levels continuously. However, isCGMs must be **scanned** in order to **view** and **store** the glucose readings. rtCGMs, on the other hand, do **not** require scanning (although being within range of the receiver/smart device is necessary).

Per the **American Diabetes Association** (ADA) 2024 Standards of Care, the following patient populations with diabetes should be offered CGMs:

- Patients receiving multiple daily insulin injections or a continuous subcutaneous infusion
- Adults receiving basal insulin

The ADA gives a higher grade of recommendation for **rtCGMs** than isCGMs.

It is important to note, when used properly, CGMs may be beneficial for **any patient** with diabetes, regardless of their A1C or medication regimen (e.g., insulin-dependent or non-insulin dependent).

For maximum benefit, rtCGMs should be used as close to **daily** as possible. isCGMs should be scanned at least once every **8 hours**.

Please note: Blood glucose testing with a **fingerstick device** should be done if diabetes symptoms or expected blood sugar levels do not match the results from a CGM. This can help confirm unexpected blood sugar readings before making treatment decisions.

Drugs that Interfere with CGM Readings

It is important to note that certain drugs can interfere with CGM readings, causing glucose readings to be falsely high or low.

Blood glucose testing with a **fingerstick device** should be done if diabetes symptoms or expected blood sugar levels do not match the results from a CGM. This can help confirm unexpected blood sugar readings before making treatment decisions.

DRUG	AFFECTED DEVICES	EFFECT
Acetaminophen (>4000 mg/day)	Dexcom G6 and G7	Causes falsely high readings
Acetaminophen (any dose)	Medtronic Guardian	Causes falsely high readings
Vitamin C (>500 mg/day)	Freestyle Libre	Causes falsely high readings
Hydroxyurea	Dexcom G6 and G7 Medtronic Guardian	Causes falsely high readings
Mannitol or sorbitol (IV or as peritoneal dialysis solution)	Senseonics Eversense	Causes falsely high readings

Adapted from Table 7.4 of the ADA Standards of Care in Diabetes - 2024

Continuous Glucose Monitors *(cont.)*

Standardized CGM Metrics and Recommendations

Although A1C presently serves as the predominant gauge for directing glucose management and as a valuable indicator of the risk of developing diabetes-related complications, the CGM metrics **time in range** (*including time spent below and above the target range*) and **glucose management indicator** offer insights that can inform a more individualized diabetes management strategy.

Time in range (TIR) has been determined to be a valuable measure for assessing glycemic control and glucose patterns. **Time above range** (TAR) and **time below range** (TBR) can be valuable indicators for adjusting insulin dosing and reassessing the treatment strategy.

The table below provides an overview of standardized CGM metrics as well as corresponding ADA recommendations.

METRIC	DESCRIPTION	RECOMMENDATIONS*
Time above range (TAR)	Percent of readings and time >250 mg/dL (<i>level 2 hyperglycemia</i>)	<5% for most adults <10% for older adults
	Percent of readings and time 181-250 mg/dL (<i>level 1 hyperglycemia</i>)	<25% for most adults <50% for older adults
Time in range (TIR)**	Percent of readings and time 70-180 mg/dL	>70% for most adults >50% for older adults
Time below range (TBR)**	Percent of readings and time 54-69 mg/dL (<i>level 1 hypoglycemia</i>)	<4% for most adults <1% for older adults
	Percent of readings and time <54 mg/dL (<i>level 2 hypoglycemia</i>)	<1%
Glycemic variability	Fluctuations in blood glucose levels	≤36%***
Glucose management indicator (GMI)	Estimate of A1C based on average CGM readings for ≥ 14 days	<7.0% (for most patients)

Adapted from Table 6.2 of the ADA Standards of Care in Diabetes - 2024
* Treatment goals must be individualized and take into consideration comorbid conditions, hypoglycemia risk and patient-specific characteristics
** A TIR >50% and TBR <1% is recommended for patients with frailty or a high risk for hypoglycemia
*** Certain studies state that targeting a lower glycemic variability (< 33%) offers an added layer of defense against hypoglycemia in individuals taking insulin or sulfonylureas

Comparison of Continuous Glucose Monitors

Reference(s): Individual manufacturer product labeling

REAL-TIME	READINGS	SENSOR	TRANSMITTER	COVERED BY MEDICARE "
Dexcom G7	Every 5 minutes	Change every 10 days	Transmitter integrated into sensor	Yes
Dexcom G6*	Every 5 minutes	Change every 10 days	Change every 3 months	Yes
Senseonics Eversense E3	Every 5 minutes	Subcutaneous implant replaced every 6 months	Charge daily (full charge time of 15 minutes)	Yes
Freestyle Libre 3**	Every 1 minute	Change every 14 days	Transmitter integrated into sensor	Yes
Medtronic Guardian Connect	Every 5 minutes	Change every 7 days	Must be charged after each sensor use so that the battery lasts 7 days (full charge time of up to 2 hours)	No***

INTERMITTENTLY SCANNED	READINGS	SENSOR	TRANSMITTER	COVERED BY MEDICARE "
Freestyle Libre 2**	Every 1 minute (scanning required)	Change every 14 days	N/A	Yes

*Compatible with Omnipod automated insulin delivery system
**Compatible with mylife Loop automated insulin delivery system
***Does not have a separate durable medical receiver for CGM (only works with app/smart device)
" Must meet Medicare coverage criteria, such as having a separate durable medical receiver for CGM

Comparison of Continuous Glucose Monitors *(cont.)*

Reference(s): Individual manufacturer product labeling

REAL-TIME	APPROVED AGES	WARM-UP TIME	APPROVED APPLICATION SITES
Dexcom G7	2 years and older	30 minutes	Back of upper arm
Dexcom G6	2 years and older	2 hours	Abdomen and back of upper arm; upper buttocks (ages 2-17 years)
Senseonics Eversense E3	18 years and older	24 hours	Back of upper arm (inserted surgically)
Freestyle Libre 3	4 years and older	1 hour	Back of upper arm
Medtronic Guardian Connect	14 to 75 years	Up to 2 hours	Abdomen and back of upper arm

INTERMITTENTLY SCANNED	APPROVED AGES	WARM-UP TIME	APPROVED APPLICATION SITES
Freestyle Libre 2**	4 years and older	1 hour	Back of upper arm

Overview of Hemoglobin A1C

Hemoglobin A1C Review

Before discussing the hemoglobin A1C (A1C) lab value itself, it is important to understand the relationship between A1C and **hemoglobin**. Hemoglobin is an iron-containing transport protein found in red blood cells. Over the lifespan of red blood cells (~120 days) the hemoglobin protein becomes **glycated** (chemically linked to sugar). The **greater** the concentration of glucose in the bloodstream, the **greater** amount of hemoglobin becomes glycated. The **A1C test** is a measurement of the **percentage** of glycated hemoglobin in the bloodstream.

Limitations of Hemoglobin A1C

It is important to note that hemoglobin A1C (A1C) is an **indirect measure** of a patient's **average** blood glucose levels. It does **not** provide information regarding glycemic **variability** (i.e., the frequency of hyper- and hypoglycemia) which is why assessing a collection of **plasma glucose** levels in **addition** to A1C is necessary to most effectively evaluate **glycemic control**.

Additionally, hemoglobin abnormalities may **falsely** increase or decrease A1C lab values. This should be considered when the reported A1C value(s) do **not** correlate with the patient's plasma glucose levels.

Conditions that may **falsely increase** A1C include:

- Anemia (due to iron, vitamin B12 and/or folic acid deficiency)
- Severe hypertriglyceridemia (> 1,750 mg/dL)
- Chronic alcohol consumption

Conditions that may **falsely decrease** A1C include:

- Acute or chronic blood loss
- Hemolytic anemia (e.g., sickle cell anemia, G6PD deficiency anemia)
- End-stage renal disease
- Pregnancy (screening should be performed using oral glucose tolerance test)

If suspected, the use of **alternative** measures of average glucose levels may be warranted (e.g., fructosamine test).

Healthy lifestyle behaviors, self-management education/support and social determinants of health should be considered in all patients.

First-line pharmacotherapy (metformin or other agents) should be selected based upon patient-specific factors (e.g., glycemic goals, cardiorenal risk, comorbidities, cost and access).

Consider **combination pharmacotherapy at initiation** if A1C $\geq 1.5\%$ above target goal.

Consider **early insulin initiation** with extreme hyperglycemia:

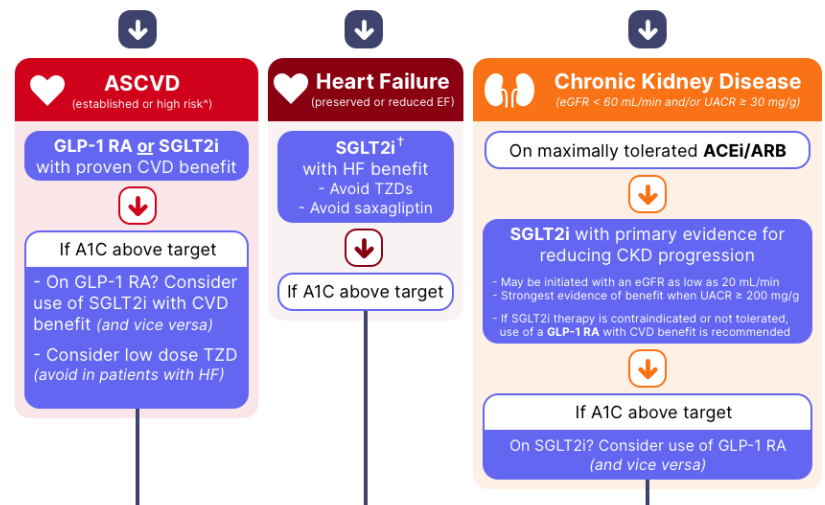
- BG ≥ 300 mg/dL
- A1C $> 10\%$
- Signs of catabolism

→ Page 2

Reassess treatment plan every **3-6 months** and modify if appropriate

Established/High-Risk of ASCVD, Heart Failure, or Chronic Kidney Disease? No

Recommended independent of baseline A1C, target A1C goal, or use of metformin



* **High-risk for ASCVD:** Typically age ≥ 55 years plus **two or more** risk factors (e.g., hypertension, obesity, smoking, dyslipidemia, albuminuria)

† SGLT2i or SGLT1/2i with proven benefit in patients with heart failure (please note: sotagliflozin is not FDA-approved for glycemic control)

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is	FDA approved CVD benefit: - canagliflozin - empagliflozin Neutral: - bexagliflozin* - dapagliflozin - ertugliflozin	FDA approved HF benefit: - dapagliflozin - empagliflozin Evidence for benefit: - canagliflozin - ertugliflozin	FDA approved renal benefit: - canagliflozin (DKD) - dapagliflozin (CKD) - empagliflozin (CKD) Neutral: - bexagliflozin* - ertugliflozin
GLP-1 RAs & GLP-1/GIP RAs	FDA approved CVD benefit: - dulaglutide - liraglutide - semaglutide (SUBQ) Neutral: - exenatide ER - lixisenatide - semaglutide (oral)	Neutral	Evidence for renal benefit: - dulaglutide - liraglutide - semaglutide (SUBQ)

Note: Sotagliflozin (SGLT1/2 inhibitor) is also a recommended option to provide heart failure benefit in patients with T2DM and heart failure. It is not recommended for glycemic control.

*FDA-approved in 2023; limited data suggests neutral cardiorenal effect. NOTE: Labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 9/2023.

Type 2 Diabetes Pharmacotherapy

Treatment Algorithm for Glycemic Control (2024 Update)

References: American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1-S321. Individual FDA Prescribing Information labels.

Page 1

Glycemic Treatment Goals	POPULATION	A1C (%)	PREPRANDIAL	2-HR PPG
Treatment goals must be individualized (and periodically reassessed) after taking into consideration comorbid conditions, hypoglycemia risk, and other patient-specific characteristics.	Most patients*	< 7.0	80 - 130 mg/dL	< 180 mg/dL
	Certain patients**	< 8.0	--	--

*More strict goals may be reasonable for certain patients, if achievable without significant hypoglycemia risk
 **Risk of severe hypoglycemia, limited life expectancy, long duration of DM, prefer a less stringent A1C goal, etc.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**.

In patients with concurrent **glycemic management** and **weight management goals**, consider therapies with **high to very high** glucose-lowering and weight-loss efficacy.



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Type 2 Diabetes Pharmacotherapy

Treatment Algorithm for Glycemic Control (2024 Update)

References: American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1-S321. Individual FDA Prescribing Information labels.



Comprehensive lifestyle changes and non-insulin agents should generally be considered prior to insulin therapy

Consider **early insulin initiation** with extreme hyperglycemia: BG ≥ 300 mg/dL, or A1C $> 10\%$ or signs of catabolism present

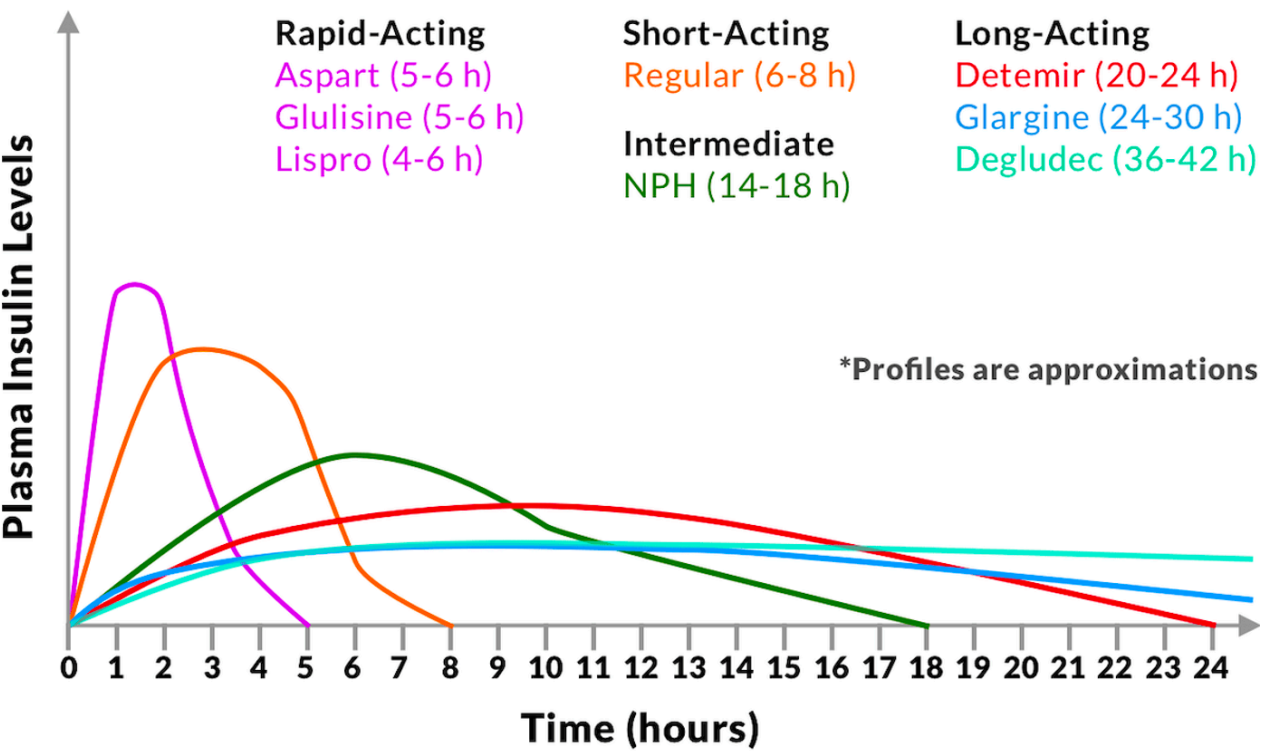
→ See Page 1 regarding non-insulin initial pharmacotherapy use and selection



Reassess treatment plan every **3-6 months** and modify if appropriate



Insulin Classes and Action Profiles



Adapted and referenced from: Hirsch IB. Insulin analogues. N Engl J Med. 2005 Jan 13;352(2):174-83. <https://www.ncbi.nlm.nih.gov/pubmed/15647580> and individual product labels.

BRAND	GENERIC	CLASS	DURATION	TYPE
Admelog	Insulin lispro (conventional)	Rapid-acting	4-6 hours	Analog
Afrezza	Inhaled insulin	Rapid-acting	2.5-3 hours	Human
Apidra	Insulin glulisine	Rapid-acting	5-6 hours	Analog
Basaglar	Insulin glargine	Long-acting	24-30 hours	Analog
Fiasp	Insulin aspart (faster-acting)	Rapid-acting	5-6 hours	Analog
HumaLog	Insulin lispro (conventional)	Rapid-acting	4-6 hours	Analog
Humulin N	NPH	Intermediate-acting	14-18 hours	Human
Humulin R (U-100)	Regular insulin	Short-acting	6-8 hours	Human
Humulin R (U-500)	Regular insulin	Intermediate-acting	~21 hours (13-24 hours)	Human
Lantus	Insulin glargine	Long-acting	24-30 hours	Analog
Levemir	Insulin detemir	Long-acting	20-24 hours	Analog
Lyumjev	Insulin lispro-aabc (faster-acting)	Rapid-acting	4-6 hours	Analog
NovoLog	Insulin aspart (conventional)	Rapid-acting	5-6 hours	Analog
Novolin N	NPH	Intermediate-acting	14-18 hours	Human
Novolin R	Regular insulin	Short-acting	6-8 hours	Human
Rezvoglar	Insulin glargine-aglr	Long-acting	24-30 hours	Analog
Semglee	Insulin glargine-yfgn	Long-acting	24-30 hours	Analog
Toujeo	Insulin glargine	Long-acting	24-30 hours	Analog
Tresiba	Insulin degludec	Long-acting	36-42 hours	Analog

Insulin Storage Requirements

All products are good until their expiration date when kept **unopened** and **refrigerated** (36°F-46°F [2°C-8°C]).

BRAND	GENERIC	DAYS GOOD AT ROOM TEMP (≤ 86°F [30°C])	STORAGE WHEN OPENED
Admelog SoloStar pen	Insulin lispro	28 days	Do not refrigerate
Admelog vial	Insulin lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Apidra SoloStar pen	Insulin glulisine	28 days (≤ 77°F [25°C])	≤ 77°F (25°C), but do not refrigerate
Apidra vial	Insulin glulisine	28 days (≤ 77°F [25°C])	Room or Refrigerated (≤ 77°F [25°C])
Basaglar KwikPen	Insulin glargine	28 days	Do not refrigerate
Fiasp FlexTouch pen	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Fiasp PenFill cartridge	Insulin aspart	28 days	Do not refrigerate
Fiasp vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humalog KwikPen	Insulin lispro	28 days	Do not refrigerate
Humalog vial	Insulin lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humalog Junior KwikPen	Insulin lispro	28 days	Do not refrigerate
Humalog TempoPen	Insulin lispro	28 days	Do not refrigerate
Humalog Mix 50/50 KwikPen	Insulin lispro protamine/lispro	10 days	Do not refrigerate
Humalog Mix 50/50 vial	Insulin lispro protamine/lispro	28 days	Do not refrigerate
Humalog Mix 75/25 KwikPen	Insulin lispro protamine/lispro	10 days	Do not refrigerate
Humalog Mix 75/25 vial	Insulin lispro protamine/lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin N KwikPen	NPH	14 days	Do not refrigerate
Humulin N vial	NPH	31 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin R vial	Regular	31 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin R U-500 KwikPen	Regular	28 days	Do not refrigerate
Humulin R U-500 vial	Regular	40 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin 70/30 KwikPen	NPH/regular	10 days	Do not refrigerate
Humulin 70/30 vial	NPH/regular	31 days	Room or Refrigerated (≤ 86°F [30°C])
Lantus SoloStar pen	Insulin glargine	28 days	Do not refrigerate
Lantus vial	Insulin glargine	28 days	Room or Refrigerated (≤ 86°F [30°C])
Levemir FlexPen	Insulin detemir	42 days	Do not refrigerate
Levemir vial	Insulin detemir	42 days	Room or Refrigerated (≤ 86°F [30°C])
Lyumjev pen	Insulin lispro-aabc	28 days	Do not refrigerate
Lyumjev vial	Insulin lispro-aabc	28 days	Room or Refrigerated (≤ 86°F [30°C])

Continued on next page →

Insulin Storage Requirements *(cont.)*

All products are good until their expiration date when kept **unopened** and **refrigerated** (36°F-46°F [2°C-8°C]).

BRAND	GENERIC	DAYS GOOD AT ROOM TEMP (≤ 86°F [30°C])	STORAGE WHEN OPENED
Novolin N FlexPen	NPH	28 days	Do not refrigerate
Novolin N vial	NPH	42 days (≤ 77°F [25°C])	≤ 77°F (25°C), but do not refrigerate
Novolin R FlexPen	Regular	28 days	Do not refrigerate
Novolin R vial	Regular	42 days (≤ 77°F [25°C])	≤ 77°F (25°C), but do not refrigerate
Novolin 70/30 FlexPen	NPH/regular	28 days	Do not refrigerate
Novolin 70/30 vial	NPH/regular	42 days (≤ 77°F [25°C])	≤ 77°F (25°C), but do not refrigerate
NovoLog FlexTouch/FlexPen	Insulin aspart	28 days	Do not refrigerate
NovoLog vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
NovoLog PenFill cartridge	Insulin aspart	28 days	Do not refrigerate
NovoLog Mix 70/30 FlexPen	Insulin aspart	14 days	Do not refrigerate
NovoLog Mix 70/30 vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Rezvoglar KwikPen	Insulin glargine-aglr	28 days	Do not refrigerate
Semglee pen	Insulin glargine-yfgn	28 days	Do not refrigerate
Semglee vial	Insulin glargine-yfgn	28 days	Room or Refrigerated (≤ 86°F [30°C])
Toujeo SoloStar pen	Insulin glargine	56 days	Do not refrigerate
Toujeo Max SoloStar pen	Insulin glargine	56 days	Do not refrigerate
Tresiba FlexTouch pen	Insulin degludec	56 days	Room or Refrigerated (≤ 86°F [30°C])
Tresiba vial	Insulin degludec	56 days	Room or Refrigerated (≤ 86°F [30°C])

Injection Areas

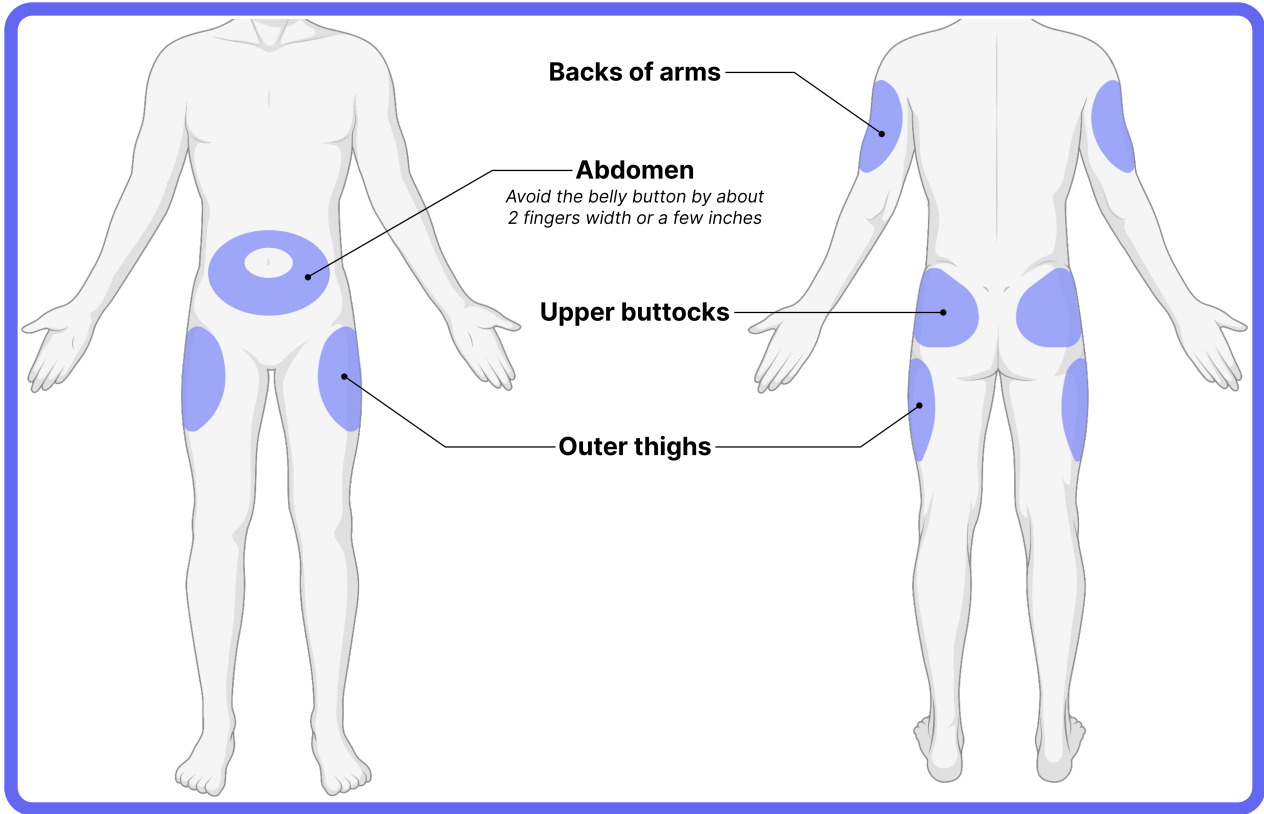
Insulin Injection Areas

Insulin is **best absorbed** when injected into the **abdomen** (staying away from the belly button by about 2 fingers width or a few inches); however, the outer thighs, upper buttocks and backs of arms are also acceptable injection areas.

Using the **same injection area** (e.g., abdomen) for each administration can help ensure the body receives **consistent levels** of insulin.

Rotate injection sites (in the same general body region) to prevent **skin damage**.

If using a **GLP-1 RA** or **GLP-1/GIP RA** with insulin, administer at **separate injection sites** and do **not** mix the medications. The injection sites may be in the same body region but should not be adjacent to each other.



GLP-1 RA and GLP-1/GIP RA Injection Areas

GLP-1 RAs and GLP-1/GIP RAs (e.g., tirzepatide) can be injected into the **abdomen** (staying away from the belly button by about 2 fingers width or a few inches), outer thighs and backs of arms.

Rotate injection sites (in the same general body region) to prevent **skin damage**.

If using a GLP-1 RA or GLP-1/GIP RA with **insulin**, administer at **separate injection sites** and do **not** mix the medications. The injection sites may be in the same body region but should **not** be adjacent to each other.

Type 2 Diabetes Drug Class Comparison

 T2DM Drug Class	 Mechanism	 Route	 A1C Lowering*	 Hypoglycemia Risk	 Weight Effect*	 Cost
Biguanides (metformin)	Decreases hepatic production of glucose; increases insulin sensitivity	Oral	● ● ●	No	 Potential for weight loss	\$
SGLT2 inhibitors	Increases urinary glucose excretion	Oral	● ●	No	 Weight loss	\$\$\$
GLP-1 receptor agonists	Increases glucose-dependent insulin release; decreases glucagon secretion; slows gastric emptying	SQ/Oral	● ● ● ● **	No	 Weight loss**	\$\$\$\$
GLP-1/GIP receptor agonists (e.g. tirzepatide)	Increases glucose-dependent insulin release; decreases glucagon secretion; slows gastric emptying	SQ	● ● ● ● ●	No	 Weight loss	\$\$\$\$\$
DPP-4 inhibitors	Increases glucose-dependent insulin release; decreases glucagon secretion	Oral	●	No	Neutral	\$\$\$
Thiazolidinediones	Increases insulin sensitivity in muscle, fat and liver cells; increases glucose entry into cells	Oral	● ●	No	 Weight gain	\$ [^]
Sulfonylureas	Stimulates insulin secretion from pancreatic beta cells	Oral	● ● ●	Yes	 Weight gain	\$
Insulin Analogs	Stimulates peripheral glucose uptake by skeletal muscle and fat tissue; inhibits hepatic glucose production	SQ	● ● ● ● ● Titrate to response	Yes	 Weight gain	\$\$\$
Human Insulin		SQ/Inhaled				\$



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SQ = subcutaneous

* The extent of A1C lowering and weight change is highly variable based upon factors including but not limited to baseline A1C, baseline weight, patient-specific characteristics, lifestyle modifications, and whether monotherapy or a multi-drug regimen is being utilized.

** The GLP-1 receptor agonists dulaglutide and subcutaneous semaglutide have notably greater A1C-lowering efficacy and weight loss effects than other GLP-1 receptor agonists.

[^] Pioglitazone is generic and has low cost; however, rosiglitazone (Avandia®), which is currently unavailable in the U.S., is not available as a generic.

References: (1) American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1–S321. (2) Individual manufacturer product labels.

Diabetes Drugs: Cardiovascular and Renal Effects

Reference(s): 1, 6-51, 58-59

DRUG/CLASS	ASCVD EFFECT	HF EFFECT	RENAL EFFECT	RENAL DOSING/USE*
Metformin Oral	Potential benefit	Neutral	Neutral	Contraindicated with eGFR < 30 mL/min
SGLT2is[†] Oral	FDA approved for CVD benefit: • canagliflozin • empagliflozin Neutral: • bexagliflozin** • dapagliflozin • ertugliflozin	FDA approved for HF benefit: • dapagliflozin • empagliflozin Evidence for benefit: • canagliflozin • ertugliflozin	FDA approved: • canagliflozin (DKD benefit) • dapagliflozin (CKD benefit) • empagliflozin (CKD benefit) Neutral: • bexagliflozin** • ertugliflozin	Renal dose adjustments necessary
GLP-1 RAs[§] SUBQ injection <i>(except oral semaglutide)</i>	FDA approved for CVD benefit: • dulaglutide • liraglutide • semaglutide (SUBQ) Neutral: • exenatide ER • lixisenatide • semaglutide (oral)	Neutral	Evidence for benefit: • dulaglutide • liraglutide • semaglutide (SUBQ)	Renal dose adjustments necessary for exenatide and lixisenatide Not necessary for dulaglutide, liraglutide, or semaglutide (oral and SUBQ); however, monitoring for adverse effects is warranted

* Review individual manufacturer's product labeling for specific renal dosing adjustments and considerations

** **Bexagliflozin** was FDA-approved in 2023 and has limited data suggesting neutral cardiorenal effect

† **Sotagliflozin** (SGLT1/2i) is a recommended option to provide heart failure benefit in patients with T2DM and heart failure (it is not approved for glycemic control)

§ **Tirzepatide** (GLP-1/GIP RA) is currently under investigation for cardiovascular and renal benefit

Diabetes Drugs: Cardiovascular and Renal Effects (cont.)

Reference(s): 1, 6-51

DRUG/CLASS	ASCVD EFFECT	HF EFFECT	RENAL EFFECT	RENAL DOSING/USE*
DPP-4is Oral	Neutral	Potential risk saxagliptin	Neutral	Renal dose adjustments necessary for alogliptin, saxagliptin and sitagliptin Not necessary for linagliptin
TZDs Oral	Potential CVD benefit: pioglitazone	Increased risk: FDA boxed warning for congestive heart failure	Neutral	Renal dose adjustments not necessary Generally not recommended in renal impairment due to the potential for fluid retention
Sulfonylureas (2nd generation) Oral	Neutral	Neutral	Neutral	<u>Glyburide</u> : Generally not recommended in renal impairment <u>Glimepiride, glipizide</u> : Use lower initial dosing and titrate carefully
Insulin Analogs SUBQ injection Human Insulin SUBQ injection, inhaled	Neutral	Neutral	Neutral	<u>Caution</u> : Lower insulin doses necessary with decreased renal function Titrate according to clinical response

* Review individual manufacturer's product labeling for specific renal dosing adjustments and considerations

Metformin: Dosing and Indications

Reference(s): 1, 25-26, 57

Metformin typically reduces A1C by **1.5-2.0%** and may promote mild weight reduction.

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Metformin IR (Glucophage)	Improved glycemic control in T2DM	Initial Dosing: 500 mg PO BID with meals, OR 850 mg PO once daily with meals Max Dosing: 2550 mg PO daily (in divided doses given with meals) Titration: Increase dose by 500 mg weekly or 850 mg every 2 weeks as tolerated for added glycemic control <i>Doses > 2000 mg daily may be given in three divided doses for improved tolerance</i>	<u>eGFR 30-45 mL/min:</u> - Initiation not recommended - Reassess risk-benefit of continued therapy <u>eGFR < 30 mL/min:</u> - Use is contraindicated - Discontinue therapy if eGFR falls below 30 mL/min <u>Hemodialysis:</u> - Use is contraindicated	Use not recommended in hepatic impairment due to concerns for lactic acidosis
Metformin ER (Glucophage XR)	Improved glycemic control in T2DM	Initial Dosing: 500 mg ER PO once daily with evening meal Max Dosing: 2000 mg ER daily (with evening meal or in divided doses with meals) Titration: Increase dose by 500 mg increments every week as tolerated for added glycemic control <i>If glycemic control is not achieved with 2000 mg ER once daily, consider 1000 mg ER twice daily (with meals)</i>	<u>eGFR 30-45 mL/min:</u> - Initiation not recommended - Reassess risk-benefit of continued therapy <u>eGFR < 30 mL/min:</u> - Use is contraindicated - Discontinue therapy if eGFR falls below 30 mL/min <u>Hemodialysis:</u> - Use is contraindicated	Use not recommended in hepatic impairment due to concerns for lactic acidosis

GLP-1 RAs and GLP-1/GIP RA: Efficacy and Safety

Reference(s): 1, 28-34, 57

GLP-1 receptor agonists typically reduce A1C by **0.7-2.1%** and can reduce body weight by 1.4-5.5 kg, depending on the individual agent and dosing utilized.
Tirzepatide (GLP-1/GIP RA) typically reduces A1C by **1.7-2.3%** and can reduce body weight by 6.3-11.2 kg, depending on the dosing utilized.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT LOWERING*	RELATIVE GI SIDE EFFECTS
Dulaglutide <i>Trulicity</i> SUBQ injection		FDA approved for CVD benefit Evidence for renal benefit		
Exenatide <i>Byetta</i> SUBQ injection		No data		
Exenatide ER <i>Bydureon, Bydureon BCise</i> SUBQ injection		Neutral CVD effect		
Liraglutide^ <i>Victoza</i> SUBQ injection		FDA approved for CVD benefit Evidence for renal benefit		
Lixisenatide <i>Adlyxin</i> SUBQ injection		Neutral CVD effect		
Semaglutide^ <i>Ozempic</i> SUBQ injection		FDA approved for CVD benefit Evidence for renal benefit		
Semaglutide <i>Rybelsus</i> Oral tablet		Neutral CVD effect		
Tirzepatide** <i>Mounjaro</i> SUBQ injection		<i>Under investigation for CVD and renal benefit</i>		

* The relative efficacies for A1C lowering and weight loss are based upon data from clinical trials included in the manufacturer's product labeling, post-marketing studies, and guidance from the American Diabetes Association: Standards of Care. The relative GI side effect profiles listed and ranked above are based upon information included in the manufacturer's product labeling. Actual patient A1C reduction, weight loss and side effect profile may differ in practice based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

** **Tirzepatide** is a dual GLP-1/GIP receptor agonist (all other drugs listed in the chart above are GLP-1 RA only).

^ Note that *Saxenda* (liraglutide), *Wegovy* (semaglutide) and *Zepbound* (tirzepatide) are approved for weight-loss in patients with/without type 2 diabetes at higher than conventional dosing for glycemic control. These specific products are intentionally excluded from this chart as they fall outside the scope of the comparison.

GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications

Reference(s): 1, 28-34

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Dulaglutide <i>Trulicity</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM Cardiovascular risk reduction <i>(in patients with T2DM plus established CVD or multiple risk factors)</i>	Initial Dosing: 0.75 mg once weekly Max Dosing: 4.5 mg once weekly Titration: • Increase to 1.5 mg/week for added glycemic control • If additional glycemic control is needed, increase the dosage in 1.5 mg increments after at least 4 weeks on the current dosage	No dose adjustment necessary	No dose adjustment necessary
Exenatide <i>Byetta</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM	Initial Dosing: 5 mcg BID (within 60 minutes of meals) Max Dosing: 10 mcg BID Titration: After 1 month of therapy, may increase to 10 mcg BID for added glycemic control	<u>CrCl < 30 mL/min:</u> Use not recommended <u>Dialysis:</u> Use not recommended	Unknown, but not expected to require dose adjustments <i>(primarily excreted renally)</i>
Exenatide ER <i>Bydureon, Bydureon BCise</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM	Initial Dosing: 2 mg ER once weekly Max Dosing: 2 mg ER once weekly	<u>eGFR < 45 mL/min:</u> Use not recommended <u>Dialysis:</u> Use not recommended	Unknown, but not expected to require dose adjustments <i>(primarily excreted renally)</i>

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications (cont.)

Reference(s): 1, 28-34

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Liraglutide <i>Victoza</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM Cardiovascular risk reduction (in patients with T2DM plus established CVD) Note: Saxenda is a higher dose liraglutide product approved for weight loss (not included here)	Initial Dosing: 0.6 mg once daily for 1 week <i>Note - the 0.6 mg dose is not effective for glycemic control and is being used to limit GI symptoms during the initial titration</i> Max Dosing: 1.8 mg daily Titration: • After 1 week of 0.6 mg daily, increase to 1.2 mg daily • If additional glycemic control is required, increase to 1.8 mg daily after at least one week of treatment with 1.2 mg daily	No dose adjustment necessary	No dose adjustment necessary
Lixisenatide <i>Adlyxin</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM	Initial Dosing: 10 mcg once daily for 14 days Max Dosing: 20 mcg daily Titration: After 14 days, increase to 20 mcg once daily	<u>eGFR 15-30 mL/min:</u> • Use with caution <u>eGFR < 15 mL/min:</u> • Use not recommended	Unknown, but not expected to require dose adjustments
Semaglutide <i>Ozempic</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM Cardiovascular risk reduction (in patients with T2DM and established CVD) Note: Wegovy is a higher dose semaglutide product approved for weight loss (not included here)	Initial Dosing: 0.25 mg once weekly for 4 weeks <i>Note - the 0.25 mg dose is not intended for glycemic control and is being used to limit GI symptoms during the initial titration</i> Max Dosing: 2 mg once weekly Titration: • After 4 weeks of 0.25 mg weekly, increase to 0.5 mg weekly • If additional glycemic control is needed after at least 4 weeks of 0.5 mg weekly, the dosage may be increased to 1 mg weekly • If additional glycemic control is needed after at least 4 weeks of 1 mg weekly, the dosage may be increased to 2 mg weekly	No dose adjustment necessary	No dose adjustment necessary

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications (cont.)

Reference(s): 1, 28-34

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Semaglutide <i>Rybelsus</i> <i>Oral tablet</i>	Improved glycemic control in T2DM	Initial Dosing: 3 mg PO once daily for 30 days <i>Note - the 3 mg dose is not effective for glycemic control and is being used to limit GI symptoms during the initial titration</i> Max Dosing: 14 mg daily Titration: • After 30 days of 3 mg daily, increase to 7 mg daily • If additional glycemic control is needed after at least 30 days on the 7 mg dose, the dosage may be increased to 14 mg daily Special Dosing Instructions: Take each dose at least 30 minutes prior to first food, beverage or oral medication(s) with no more than 4 oz of plain water	No dose adjustment necessary	No dose adjustment necessary
Tirzepatide <i>Mounjaro</i> <i>GLP-1/GIP RA</i> <i>SUBQ injection</i>	Improved glycemic control in T2DM	Initial Dosing: 2.5 mg once weekly for 4 weeks <i>Note - the 2.5 mg dose is not intended for glycemic control and is being used to limit GI symptoms during the initial titration</i> Max Dosing: 15 mg once weekly Titration: • After 4 weeks of 2.5 mg weekly, increase to 5 mg weekly • If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose	No dose adjustment necessary	No dose adjustment necessary

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

SGLT2 Inhibitors: Efficacy and Safety

Reference(s): 3-5, 40-44, 61-63

SGLT2 inhibitors typically reduce A1C by **0.5-1.0%** and can reduce body weight by ~3 kg.

DRUG†	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT LOWERING*	SAFETY CONCERNS
Bexagliflozin <i>Brenzavvy</i>		<i>Limited data suggests neutral effect; however, additional trials are needed</i>		• Increased urinary frequency • Volume depletion • Urinary tract infections • Genital mycotic infections • Fournier’s gangrene
Canagliflozin <i>Invokana</i>		FDA approved for CVD benefit FDA approved for DKD benefit Evidence for HF benefit		
Dapagliflozin <i>Farxiga</i>		FDA approved for HF benefit FDA approved for CKD benefit Neutral CVD effect		
Empagliflozin <i>Jardiance</i>		FDA approved for CVD benefit FDA approved for HF benefit FDA approved for CKD benefit		
Ertugliflozin <i>Steglatro</i>		Neutral CVD effect Neutral renal effect Evidence for HF benefit		

* These relative efficacy points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight loss in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

† Sotagliflozin (SGLT1/2i) is a recommended option to provide heart failure benefit in patients with T2DM and heart failure (it is not approved for glycemic control). For this reason it is not included in this table.

SGLT2 Inhibitors: Dosing and Indications

Reference(s): 35-40

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Bexagliflozin <i>Brenzavvy</i>	T2DM: improved glycemic control	Initial Dosing: 20 mg PO once daily in the morning Max Dosing: 20 mg daily	<u>eGFR < 30 mL/min:</u> • Not recommended <u>Dialysis:</u> Use is contraindicated	<u>Mild to moderate impairment:</u> No dose adjustment necessary <u>Severe impairment:</u> Not studied, not recommended
Canagliflozin <i>Invokana</i>	T2DM: improved glycemic control Cardiovascular risk reduction <i>(in patients with T2DM & established CVD)</i> Renal risk reduction <i>(in patients with T2DM & diabetic nephropathy)</i>	Initial Dosing: 100 mg PO once daily <i>(take before 1st meal of the day)</i> Max Dosing: 300 mg daily Titration: May increase to 300 mg daily for added glycemic control	<u>eGFR < 60 mL/min:</u> Limit to 100 mg daily <u>eGFR < 30 mL/min:</u> • Initiation not recommended • Not recommended for glycemic control • May continue at 100 mg daily for renal risk reduction <u>Dialysis:</u> Use is contraindicated	<u>Mild to moderate impairment:</u> No dose adjustment necessary <u>Severe impairment:</u> Not studied, not recommended
Dapagliflozin <i>Farxiga</i>	T2DM: improved glycemic control Heart failure risk reduction <i>(in patients with or without T2DM)</i> Renal risk reduction <i>(in patients with CKD with or without T2DM)</i>	Initial Dosing: • 5 mg PO once daily <i>(for glycemic control)</i> • 10 mg PO once daily <i>(for heart failure or renal risk reduction)</i> Max Dosing: 10 mg daily Titration: May increase to 10 mg daily for added glycemic control <i>(no titration for heart failure or renal risk reduction indications)</i>	<u>eGFR < 45 mL/min:</u> Not recommended for glycemic control <u>eGFR < 25 mL/min:</u> • Initiation not recommended • Use for other indications (e.g., heart failure, chronic kidney disease) may continue at 10 mg daily <u>Dialysis:</u> Use is contraindicated	No dose adjustment necessary However, use in severe impairment has not been studied <i>(use with caution)</i>
Empagliflozin <i>Jardiance</i>	T2DM: improved glycemic control Cardiovascular risk reduction <i>(in patients with T2DM & established CVD)</i> Heart failure risk reduction <i>(in patients with or without T2DM)</i> Renal risk reduction <i>(in patients with CKD with or without T2DM)</i>	Initial Dosing: 10 mg PO once daily in the morning Max Dosing: 25 mg daily Titration: May increase to 25 mg daily for added glycemic control	<u>eGFR < 30 mL/min:</u> • Not recommended for glycemic control • Insufficient data to specify dosing for CV risk reduction <u>eGFR < 20 mL/min:</u> • Insufficient data to specify dosing for HF/CKD risk reduction <u>Dialysis:</u> Use is contraindicated	No dose adjustment necessary
Ertugliflozin <i>Steglatro</i>	T2DM: improved glycemic control	Initial Dosing: 5 mg PO once daily in the morning Max Dosing: 15 mg daily Titration: May increase to 15 mg daily for added glycemic control	<u>eGFR < 45 mL/min:</u> Use not recommended <u>Dialysis:</u> Use is contraindicated	<u>Mild to moderate impairment:</u> No dose adjustment necessary <u>Severe impairment:</u> Not studied, not recommended
Sotagliflozin <i>Inpefa</i>	CV and HF risk reduction <i>(in patients with HF or patients with T2DM, CKD and CV risk factors)</i>	Initial Dosing: 200 mg PO once daily not more than 1 hour before 1st meal of the day Max Dosing: 400 mg daily Titration: Up-titrate after at least 2 weeks to 400 mg, as tolerated	Dose adjustments not specified (use with caution)	<u>Mild impairment:</u> No dose adjustment necessary <u>Moderate to severe impairment:</u> Not studied, not recommended

DPP-4 Inhibitors: Efficacy and Safety

Reference(s): 1, 41-44, 57

DPP-4 inhibitors typically reduce A1C by **0.5-0.9%** and are weight neutral.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT LOWERING*	SAFETY CONCERNS
Alogliptin <i>Nesina</i>	●	Neutral cardiovascular effect Neutral renal effect Evidence for heart failure risk: saxagliptin	Neutral effect	- Pancreatitis - Heart failure - Arthralgia
Linagliptin <i>Tradjenta</i>	●			
Saxagliptin <i>Onglyza</i>	●			
Sitagliptin <i>Januvia</i>	●			

* These relative efficacy points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight loss in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

DPP-4 Inhibitors: Dosing and Indications

Reference(s): 41-44

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Alogliptin <i>Nesina</i>	Improved glycemic control in T2DM	Initial Dosing: 25 mg PO once daily <i>(dosed renally)</i> Max Dosing: 6.25 mg to 25 mg daily <i>(dependent on renal function)</i>	<u>CrCl 30 to < 60 mL/min:</u> 12.5 mg once daily <u>CrCl < 30 mL/min:</u> 6.25 mg once daily <u>Hemodialysis:</u> 6.25 mg once daily <i>(administer without regard to timing of hemodialysis)</i>	<u>Mild to moderate impairment:</u> No dose adjustment necessary <u>Severe impairment:</u> Insufficient data Pharmacokinetics Pearl: <i>Alogliptin is not extensively metabolized and drug levels are not expected to be meaningfully impacted (use with caution)</i>
Linagliptin <i>Tradjenta</i>	Improved glycemic control in T2DM	Initial Dosing: 5 mg PO once daily Max Dosing: 5 mg daily	No dose adjustment necessary	No dose adjustment necessary
Saxagliptin <i>Onglyza</i>	Improved glycemic control in T2DM	Initial Dosing: 2.5 mg to 5 mg PO once daily <i>(dosed renally)</i> Max Dosing: 2.5 mg to 5 mg daily <i>(dependent on renal function)</i>	<u>eGFR < 45 mL/min:</u> 2.5 mg once daily <u>Hemodialysis:</u> 2.5 mg once daily <i>(administer after hemodialysis)</i>	No dose adjustment necessary
Sitagliptin <i>Januvia</i>	Improved glycemic control in T2DM	Initial Dosing: 100 mg PO once daily <i>(dosed renally)</i> Max Dosing: 25 mg to 100 mg daily <i>(dependent on renal function)</i>	<u>eGFR 30 mL/min to <45 mL/min:</u> 50 mg once daily <u>eGFR < 30 mL/min:</u> 25 mg once daily <u>Dialysis:</u> 25 mg once daily <i>(administer without regard to timing of dialysis)</i>	<u>Mild to moderate impairment:</u> No dose adjustment necessary <u>Severe impairment:</u> Insufficient data Pharmacokinetics Pearl: <i>Sitagliptin is not extensively metabolized and drug levels are not expected to be meaningfully impacted (use with caution)</i>

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

Sulfonylureas: Efficacy and Safety

Reference(s): 1, 45-49, 57, 60

Sulfonylureas typically reduce A1C by **1.5-2.0%** and can cause weight gain of ~1-2 kg.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE HYPOGLYCEMIA RISK*	RELATIVE WEIGHT GAIN*
Glipizide <i>Glucotrol, Glucotrol XL</i>		Neutral cardiovascular effect Neutral renal effect: <i>Use caution with renal impairment due to increased risk for hypoglycemia (particularly with the ER tablet)</i>	Immediate-release:  <i>Glipizide is a short-acting sulfonylurea and is currently listed on the Beers Criteria as a preferred option to long-acting sulfonylureas (use with extreme caution in elderly patients)</i> Extended-release: 	
Glimepiride <i>Amaryl</i>		Neutral cardiovascular effect Neutral renal effect: <i>Use caution with renal impairment due to increased risk for hypoglycemia</i>	 <i>Glimepiride is a long-acting sulfonylurea and is currently listed on the Beers Criteria (use with extreme caution in elderly patients)</i>	
Glyburide <i>Diabeta, Glynase PresTab, Micronase</i>		Neutral cardiovascular effect Neutral renal effect: <i>Generally not recommended with renal impairment due to increased risk for hypoglycemia</i>	 <i>Glyburide is a long-acting sulfonylurea with renally excreted active metabolites and is currently listed on the Beers Criteria (use with extreme caution in elderly patients)</i>	

* These relative efficacy and risk points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight gain in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

Sulfonylureas: Dosing and Indications

Reference(s): 45-49

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Glipizide <i>Glucotrol</i>	Improved glycemic control in T2DM	Initial Dosing: 5 mg PO once daily 30 minutes prior to breakfast <i>Consider lower initial dose (2.5 mg daily) in patients at increased risk for hypoglycemia</i> Max Dosing: 40 mg daily <i>(daily doses > 15 mg should be divided)</i> Titration: May adjust dose in 2.5-5 mg increments for added glycemic control <i>(no more frequently than every several days)</i>	Use lower initial dosing and titrate carefully Pharmacokinetics Pearl: Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) <u>Dialysis:</u> Dose adjustments not specified in prescribing information Pharmacokinetics Pearl: Glipizide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dosing and titrate carefully Pharmacokinetics Pearl: As glipizide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)
Glipizide ER <i>Glucotrol XL</i>	Improved glycemic control in T2DM	Initial Dosing: 5 mg ER PO once daily with breakfast (or first main meal) <i>Consider lower initial dose (2.5 mg ER daily) in patients at increased risk for hypoglycemia</i> Max Dosing: 20 mg ER daily Titration: Dose adjustments can be made according to glycemic control	Use lower initial dosing and titrate carefully Pharmacokinetics Pearl: Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) <u>Dialysis:</u> Dose adjustments not specified in prescribing information Pharmacokinetics Pearl: Glipizide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dosing and titrate carefully Pharmacokinetics Pearl: As glipizide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)
Glimepiride <i>Amaryl</i>	Improved glycemic control in T2DM	Initial Dosing: 1-2 mg PO once daily with breakfast (or first main meal) <i>Consider lower initial dose (1 mg daily) in patients at increased risk for hypoglycemia</i> Max Dosing: 8 mg daily Titration: May adjust dose in 1-2 mg increments for added glycemic control <i>(no more frequently than every 1-2 weeks)</i>	Use lower initial dose (1 mg) in patients with renal impairment and titrate carefully Pharmacokinetics Pearl: Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) <u>Dialysis:</u> Dose adjustments not specified in prescribing information Pharmacokinetics Pearl: Glimepiride is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Dose adjustments not specified in prescribing information due to lack of adequate studies Pharmacokinetics Pearl: As glimepiride is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)

Sulfonylureas: Dosing and Indications (cont.)

Reference(s): 45-49, 56

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Glyburide <i>Diabeta, Micronase</i>	Improved glycemic control in T2DM	Initial Dosing: 2.5 mg to 5 mg PO once daily with breakfast (or first main meal) <i>Consider lower initial dose (1.25 mg daily) in patients at increased risk for hypoglycemia</i> Max Dosing: 20 mg daily <i>(single or divided dosing)</i> <i>Consider BID dosing when daily dose > 10 mg</i> Titration: Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals according to glycemic control	Use lower initial dose (1.25 mg) in patients with renal impairment and titrate carefully Pharmacokinetics Pearl: Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information Pharmacokinetics Pearl: Glyburide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dose (1.25 mg) in patients with hepatic impairment (titrate cautiously) Pharmacokinetics Pearl: As glyburide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)
Glyburide, micronized <i>Glynase PresTab</i> <i>PresTabs are not bioequivalent to glyburide tablets</i>	Improved glycemic control in T2DM	Initial Dosing: 1.5 mg to 3 mg PO once daily with breakfast (or first main meal) <i>Consider lower initial dose (0.75 mg daily) in patients at increased risk for hypoglycemia</i> Max Dosing: 12 mg daily <i>(single or divided dosing)</i> <i>Consider BID dosing when daily dose > 6 mg</i> Titration: Dosage increases should be made in increments of no more than 1.5 mg at weekly intervals according to glycemic control	Use lower initial dose (0.75 mg) in patients with renal impairment and titrate carefully Pharmacokinetics Pearl: Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information Pharmacokinetics Pearl: Glyburide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dose (0.75 mg) in patients with hepatic impairment (titrate cautiously) Pharmacokinetics Pearl: As glyburide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)

Thiazolidinediones: Efficacy and Safety

Reference(s): 1, 50-51, 57

Thiazolidinediones typically reduce A1C by **1.0-1.5%** and can cause weight gain of ~4 kg.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT GAIN*	OTHER CONSIDERATIONS
Pioglitazone <i>Actos</i>		Increased heart failure risk Potential cardiovascular benefit Neutral renal effect: <i>Generally not recommended with renal impairment due to increased risk for fluid retention</i>		Congestive heart failure risk Risk for bladder cancer Risk for fluid retention Risk for bone fracture
Rosiglitazone <i>Avandia</i>		Increased heart failure risk Neutral cardiovascular effect Neutral renal effect: <i>Generally not recommended with renal impairment due to increased risk for fluid retention</i>		Congestive heart failure risk Increased LDL levels Risk for fluid retention Risk for bone fracture Brand only (\$\$\$)

* These relative efficacy and risk points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight gain in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

Thiazolidinediones: Dosing and Indications

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Pioglitazone <i>Actos</i>	Improved glycemic control in T2DM	Initial Dosing: 15 mg to 30 mg PO once daily <i>A lower initial dose of 15 mg recommended in patients with congestive HF (NYHA class I or II)</i> Max Dosing: 45 mg daily Titration: May increase dose in 15 mg increments according to glycemic control	No dose adjustment necessary <i>Generally not recommended with renal impairment due to increased risk for fluid retention</i>	No dose adjustment necessary
Rosiglitazone <i>Avandia</i>	Improved glycemic control in T2DM	Initial Dosing: 4 mg PO daily (<i>as single or two divided doses</i>) Max Dosing: 8 mg daily Titration: After 8-12 weeks, the dose may be increased to 8 mg daily for added glycemic control	No dose adjustment necessary <i>Generally not recommended with renal impairment due to increased risk for fluid retention</i>	Dose adjustments not specified in prescribing information: <i>However, rosiglitazone should not be used in patients with evidence of active liver disease or ALT levels > 2.5 times the upper limit of normal</i>

Drugs that Cause Hyperglycemia

CATEGORY	EXAMPLES
Atypical antipsychotics	Most risk Clozapine, olanzapine Intermediate risk Iloperidone, paliperidone, quetiapine, risperidone Least risk Aripiprazole, ziprasidone
Beta-blockers*^	Atenolol, metoprolol, propranolol
Systemic corticosteroids	Methylprednisolone, prednisone, prednisolone
Immunosuppressants	Cyclosporine, sirolimus, tacrolimus
Protease inhibitors	Atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Quinolones*	Ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin
Thiazide-type diuretics	Chlorothiazide, chlorthalidone, hydrochlorothiazide, indapamide, metolazone

*Also known to cause hypoglycemia
^Carvedilol and nebivolol are not associated with hyperglycemia

Drugs that Cause Hypoglycemia

CATEGORY	EXAMPLES
ACE inhibitors	Benazepril, enalapril, lisinopril, ramipril, quinapril, etc.
Alcohol	Alcoholic beverages
Antiarrhythmics	Cibenzoline, disopyramide, quinidine
Quinolone antibiotics*	Ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin
Antibiotics (misc.)	Chloramphenicol, chloroquine, linezolid, pentamidine
Antidiabetics	All drugs for type 2 diabetes work to lower blood sugars; there is notable hypoglycemia risk with insulins, sulfonylureas, thiazolidinediones, and when combining multiple agents
Beta-blockers*	Nadolol, propranolol, sotalol, timolol
Anti-obesity drug	Lorcaserin
Salicylates	Aspirin, magnesium salicylate, salsalate

*Also known to cause hyperglycemia

Hypoglycemia Classification & Treatment

Symptoms of **hypoglycemia** include, but are not limited to:

- Hunger
- Irritability
- Shakiness
- Tachycardia

If allowed to progress hypoglycemia can lead to loss of consciousness. In **severe cases**, hypoglycemia may lead to seizure, coma and death.

All patients should be screened for their risk of hypoglycemia as well as for any **impaired awareness** of hypoglycemia. A patient’s history of hypoglycemia should be reviewed and evaluated during **each** and **every** clinical encounter.

Those with **reduced** hypoglycemia awareness should be **referred** to a trained healthcare professional in order to re-establish **awareness** of the appropriate signs and symptoms of hypoglycemia. If impaired or declining cognitive function is suspected/found, routine assessment with an added emphasis on identifying and preventing hypoglycemia is warranted.

If a patient experiences a **Level 2** hypoglycemic event **without** any reported symptoms it is likely they have impaired hypoglycemia awareness.

Careful consideration of a patient’s risk for hypoglycemia is warranted when selecting or adjusting glycemic goals and glucose-lowering therapy.

Continuous glucose monitoring (CGM) devices have been shown to be effective in reducing the incidence of hypoglycemia and are useful for revealing asymptomatic episodes in patients receiving insulin therapy. CGMs are recommended for those at a **high-risk** for hypoglycemia.

Classification of Hypoglycemia

CATEGORY	GLYCEMIC CRITERIA/DESCRIPTION
Level 1	Glucose <70 mg/dL and ≥54 mg/dL
Level 2	Glucose <54 mg/dL
Level 3	Severe event characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia

Recreated from Table 6.4 of the ADA Standards of Care in Diabetes – 2024

Treatment of Hypoglycemia

The preferred treatment for **hypoglycemia** (BG <70 mg/dL) in **conscious** patients is 15-20 grams of **oral glucose** (or any form of fast-acting carbohydrate containing glucose). The treatment should be repeated **15 minutes later** if hypoglycemia persists.

Patients receiving **insulin** or those who are at a **high-risk** for hypoglycemia should be prescribed **glucagon** (available as nasal spray and injection). A preparation that does **not** require reconstitution is preferred. All patients and caregivers should be instructed on proper use.

In the event of **one or more** Level 2 or 3 hypoglycemic episodes, the patient’s glucose-lowering regimen should be re-evaluated with consideration for de-intensifying therapy or switching to agents with a lower risk for hypoglycemia.

Counsel patients on the importance of **correcting** hypoglycemic episodes.

- The potential risks resulting from short-term *hyperglycemia* are **insignificant** compared to the clear risks and consequences of **untreated hypoglycemia**

References

1. American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S1–S321.
2. Lajthia E, Buceit JD, Nadpara PA, et al. Combination therapy with once-weekly glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a case series. Pharm Pract (Granada). 2019;17(4):1588. doi:10.18549/PharmPract.2019.4.1588
3. Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med. 2014;29(2):388-394.
4. Hirsch IB. Insulin analogues. N Engl J Med. 2005 Jan 13;352(2):174-83.
5. Wells BG, DiPiro JT, Schwinghammer TL, DiPiro CV. Pharmacokinetics of select insulins administered subcutaneously - Table 19-3. Pharmacotherapy Handbook, Tenth Edition.
6. ADMELOG - insulin lispro injection, solution. Sanofi-Aventis U.S. LLC Accessed via DailyMed. Updated November 30, 2020.
7. AFREZZA - insulin human powder, metered AFREZZA - insulin human kit. Mannkind Corporation. Accessed via DailyMed. Updated March 22, 2021.
8. APIDRA - insulin glulisine injection, solution APIDRA SOLOSTAR- insulin glulisine injection, solution. Sanofi-Aventis U.S. LLC Accessed via DailyMed. Updated January 3, 2019.
9. BASAGLAR KWIKPEN - insulin glargine injection, solution BASAGLAR TEMPO PEN - insulin glargine injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated September 27, 2021.
10. FIASP - insulin aspart injection injection, solution. Novo Nordisk. Accessed via DailyMed. Updated December 19, 2019.
11. HUMALOG- insulin lispro injection, solution HUMALOG KWIKPEN - insulin lispro injection, solution HUMALOG JUNIOR KWIKPEN - insulin lispro injection, solution HUMALOG TEMPO PEN - insulin lispro injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated May 3, 2021.
12. HUMULIN N - insulin human injection, suspension STERILE DILUENT - diluent injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated June 27, 2022.
13. HUMULIN R - insulin human injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated June 27, 2022.
14. HUMULIN R U-500 - insulin human injection, solution HUMULIN R U-500 KWIKPEN - insulin human injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated June 27, 2022.
15. LANTUS - insulin glargine injection, solution LANTUS SOLOSTAR - insulin glargine injection, solution. Sanofi-Aventis U.S. LLC Accessed via DailyMed. Updated January 27, 2021.
16. LEVEMIR - insulin detemir injection, solution. Novo Nordisk. Accessed via DailyMed. Updated July 1, 2022.
17. LYUMJEV - insulin lispro-aabc injection, solution LYUMJEV KWIKPEN - insulin lispro-aabc injection, solution LYUMJEV JUNIOR KWIKPEN - insulin lispro-aabc injection, solution LYUMJEV TEMPO PEN- insulin lispro-aabc injection, solution LYUMJEV KWIKPEN - insulin lispro-aabc injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated August 13, 2021.
18. NOVOLOG - insulin aspart injection, solution INSULIN DILUTING MEDIUM FOR NOVOLOG - water injection injection, solution. Novo Nordisk. Accessed via DailyMed. Updated October 22, 2021.
19. NOVOLIN N - human insulin injection, suspension. Novo Nordisk. Accessed via DailyMed. Updated November 15, 2019.
20. NOVOLIN R- human insulin injection, solution. Novo Nordisk. Accessed via DailyMed. Updated November 15, 2019.
21. SEMGLEE - insulin glargine injection, solution. Mylan Specialty L.P. Accessed via DailyMed. Updated June 8, 2020.
22. REZVOGLAR KWIKPEN- insulin glargine-aglr injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated November 16, 2022.
23. TOUJEO - insulin glargine injection, solution TOUJEO MAX - insulin glargine injection, solution. Sanofi-Aventis U.S. LLC Accessed via DailyMed. Updated December 3, 2020.
24. TRESIBA - insulin degludec injection, solution. Novo Nordisk. Accessed via DailyMed. Updated July 1, 2022.
25. METFORMIN HYDROCHLORIDE tablet. ACI Healthcare USA, Inc. Accessed via DailyMed. Updated December 26, 2020.
26. METFORMIN ER 500 MG tablet, METFORMIN ER 750 MG tablet. Granules India Ltd. Accessed via DailyMed. Updated April 5, 2021.
27. TRULICITY - dulaglutide injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated June 10, 2022.
28. BYETTA - exenatide injection. AstraZeneca Pharmaceuticals LP. Accessed via DailyMed. Updated June 10, 2022.
29. BYDUREON - exenatide injection, suspension, extended release BYDUREON - exenatide kit. AstraZeneca Pharmaceuticals LP. Accessed via DailyMed. Updated July 26, 2022.
30. VICTOZA - liraglutide injection. Novo Nordisk. Accessed via DailyMed. Updated June 10, 2022.

References

31. ADLYXIN - lixisenatide kit ADLYXIN - lixisenatide injection solution. Sanofi-Aventis U.S. LLC Accessed via DailyMed. Updated June 17, 2022.

32. OZEMPIC- semaglutide injection, solution. Novo Nordisk. Accessed via DailyMed. Updated March 28, 2022.

33. RYBELSUS - oral semaglutide tablet. Novo Nordisk. Accessed via DailyMed. Updated June 10, 2022.

34. MOUNJARO - tirzepatide injection, solution. Eli Lilly and Company. Accessed via DailyMed. Updated May 13, 2022.

35. INVOKANA - canagliflozin tablet, film coated. Janssen Pharmaceuticals, Inc. Accessed via DailyMed. Updated November 9, 2021.

36. FARXIGA - dapagliflozin tablet, film coated. AstraZeneca Pharmaceuticals LP. Accessed via DailyMed. Updated July 11, 2022.

37. JARDIANCE - empagliflozin tablet, film coated. Boehringer Ingelheim Pharmaceuticals, Inc. Accessed via DailyMed. Updated March 23, 2022.

38. STEGLATRO - ertugliflozin tablet, film coated. Merck Sharp & Dohme LLC. Accessed via DailyMed. Updated May 20, 2022.

39. BRENZAVVY - bexagliflozin tablet. TheracosBio, LLC. Accessed via DailyMed. Updated September 18, 2023.

40. INPEFA - sotagliflozin tablet. Lexicon Pharmaceuticals, Inc. Accessed via DailyMed. Updated November 2, 2023.

41. NESINA - alogliptin tablet, film coated. Takeda Pharmaceuticals America, Inc. Accessed via DailyMed. Updated March 17, 2022.

42. TRADJENTA - linagliptin tablet, film coated. Boehringer Ingelheim Pharmaceuticals, Inc. Accessed via DailyMed. Updated April 21, 2022.

43. ONGLYZA - saxagliptin tablet, film coated. AstraZeneca Pharmaceuticals LP. Accessed via DailyMed. Updated October 24, 2019.

44. JANUVIA - sitagliptin tablet, film coated. Merck Sharp & Dohme LLC. Accessed via DailyMed. Updated July 22, 2022.

45. GLIPIZIDE tablet. Mylan Pharmaceuticals Inc. Accessed via DailyMed. Updated April 7, 2022.

46. GLIPIZIDE tablet, extended release. Zydus Pharmaceuticals USA Inc. Accessed via DailyMed. Updated November 9, 2022.

47. GLIMEPIRIDE tablet. Aurobindo Pharma Limited. Accessed via DailyMed. Updated November 8, 2022.

48. GLYBURIDE tablet. Zydus Lifesciences Limited. Accessed via DailyMed. Updated November 16, 2022.

49. GLYNASE - glyburide tablet. Pharmacia and Upjohn Company LLC. Accessed via DailyMed. Updated October 7, 2017.

50. ACTOS - pioglitazone tablet. Takeda Pharmaceuticals America, Inc. Accessed via DailyMed. Updated December 16, 2021.

51. AVANDIA 2MG- rosiglitazone maleate tablet, film coated, AVANDIA 4MG- rosiglitazone maleate tablet, film coated. GlaxoSmithKline LLC. Accessed via DailyMed. Updated November 2020.

52. American Diabetes Association. Insulin Administration. Diabetes Care 2003 Jan; 26(suppl 1): s121-s124. <https://doi.org/10.2337/diacare.26.2007.S121>

53. Rehman A, Setter SM, Vue MH. Drug-Induced Glucose Alterations Part 2: Drug-Induced Hyperglycemia. Diabetes Spectrum 2011 Nov; 24(4): 234-238.

54. Vue MH, Setter SM. Drug-Induced Glucose Alterations Part 1: Drug-Induced Hypoglycemia. Diabetes Spectrum 2011 Aug; 24(3): 171-177.

55. Drug-induced low blood sugar. Medline Plus - U.S. National Library of Medicine. Page last updated: 04 February 2020.

56. By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023;71(7):2052-2081. doi:10.1111/jgs.18372

57. Trujillo J, Haines S. Diabetes Mellitus. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Michael Posey LL. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw Hill; 2023. Accessed January 26, 2023.

58. Patoulas D, Dimosiari A. Meta-analysis Addressing the Cardiovascular Safety of Bexagliflozin in Patients With Type 2 Diabetes Mellitus. Am J Cardiol. 2022;178:178-179. doi:10.1016/j.amjcard.2022.05.005

59. Allegretti AS, Zhang W, Zhou W, et al. Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD. Am J Kidney Dis. 2019;74(3):328-337. doi:10.1053/j.ajkd.2019.03.417

60. Riddle, M., & Ahmann, A. (2020). Therapeutics of Type 2 Diabetes Mellitus. In Williams Textbook of Endocrinology (Fourteenth ed., pp. 1371-1402.e9).

61. Clinical Management Topics: Learning How to Inject Insulin. Association of Diabetes Care & Education Specialists. 2020. Retrieved February 2, 2023.

62. Clinical Management Topics: Using GLP-1 Receptor Agonists. Association of Diabetes Care & Education Specialists. 2020. Retrieved February 2, 2023.

63. Figures created with BioRender.com